Clinical review

Fortnightly review

Gallbladder disease

Malcolm C Bateson

Gall stones are very common and their prevalence increases appreciably with age; it is also determined by sex, body weight, and race. Fortunately, most gall stones do not cause severe symptoms such as colic and jaundice. They are best detected by ultrasonography, although endoscopic retrograde cholangiopancreatography and magnetic resonance scanning may be required for duct stones.

Troublesome gall stones are generally treated by cholecystectomy, and two thirds of these procedures are carried out by laparoscopy. Duct stones may be treated with endoscopic retrograde pancreatography, sphincterotomy, and extraction, or by open choledochotomy. Dissolution with ursodeoxycholic acid may be a useful reserve treatment for some patients. Persistent symptoms after surgery are common and are sometimes difficult to treat.

Summary points

- Operations to remove gall stones have become more common, probably because indications for these have changed
- 70% of stones in the gall bladder do not cause symptoms
- Cholecystectomy relieves pain, but 50% of patients still have digestive symptoms afterwards
- Laparoscopic cholecystectomy has not reduced overall morbidity, mortality, or the cost of surgery because operations are now carried out in people who are older and less fit

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BMJ 1999;318:1745–8

Gallbladder disease

Why we have a gall bladder at all is something of a mystery. Many animals such as horses, pigeons, and rats manage quite well without one. The gall bladder functions as an optional store and concentrator for the bile secreted by the liver. Bile acids are important in rendering the fats in the intestine soluble before their digestion and absorption. The gall bladder contracts to eject high concentrations of bile into the duodenum when a fatty meal is consumed—but it does the same thing when any other sort of meal is taken or even when water is drunk. The gall bladder is clearly not essential to human digestion since patients who have had a cholecystectomy have no problems in this regard. In fact, sometimes it seems as if its main role is to keep doctors busy.

In addition to bile acids, the liver secretes cholesterol and bilirubin into the bile, and herein lies the main problem. Cholesterol is not always in stable solution, even in perfectly healthy people, and can crystallise to form stones. In addition, the soluble conjugated bilirubin may be converted to free bilirubin, which then precipitates. The bile in the gall bladder is therefore an unstable concentrated "soup of chemical problems."

It is the presence of stones in the gall bladder that explains almost all of the ills inflicted by this organ. The process of stone formation is thought to be the result of a triple defect:

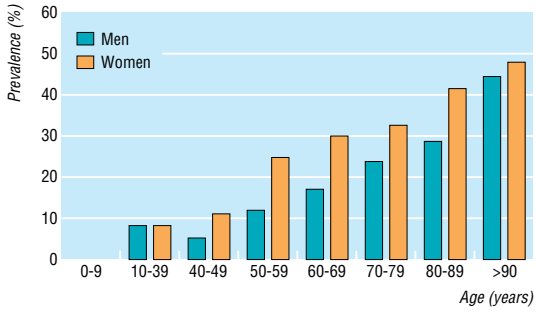
- Patients with gall stones have even more unstable bile than the rest of us
- They have more sluggish activity of the gall bladder, which allows crystals to grow into large stones
- They are also more prone to nucleate crystals in the first place, thereby initiating the process.

The major component of gall stones is cholesterol, which the liver clears from the body via the biliary tract and intestine, but bilirubin pigment on its own can form stones, and calcium salts also join in the process to a varying degree.

Who gets gallbladder disease?

The prevalence of gall stones in the population can be measured conveniently by ultrasonography,[1 2] and the prevalence of gallbladder disease is taken as the sum of people with gall stones and those who have had a cholecystectomy. An alternative technique is necropsy survey,[3–7] which gives the same figures, but with little information about symptoms during life.

Gallstone disease has become more common in Britain in the second half of the 20th century.[8–10] This is partly because of the ageing population, but probably for other reasons too, such as increasing obesity in the population (figure). Doctors who believe that gall stones are a disease of middle aged women are mistaken. Though women have more stones at every age, and 11% of women in their 40s have stones, this is



Prevalence of gallstone disease in modern Britain

a lower proportion than the 45% of men in their 90s who have gall stones.

Pregnancy increases the risk of gall stones, but the oral contraceptive pill does not.[11] Although there is evidence that the high doses of oestrogens found in hormone replacement therapy may cause stones, we do not yet have definite proof that this is the case. There is general agreement that obesity causes stones.[12 13] Certainly morbid obesity (body mass index >40) is strongly linked with stones, but even more so is the rapid weight reduction caused by a stringent diet or bariatric surgery.[14] Otherwise the connection between diet and gall stones is not completely clear. No particular food has been incriminated in the formation of stones. Nevertheless, vegetarians have fewer stones,[15] and the modest quantities of alcohol that protect from ischaemic heart disease also reduce the risk of gall stones.[16 17] It has also been proposed that moderate quantities of exercise, aspirin, and non-steroidal anti-inflammatory drugs are protective.

There is an international league table of gallstone prevalence (table). The United States provides the best information about ethnic differences. Native Americans have the highest rates (in fact they have a higher prevalence than any other group in the world); next come people of Hispanic origin, then white people, and the lowest rates of all are seen in the black population. Gallstone disease tends to be a disease of more affluent societies, but there are clearly racial differences. However, the prevalence of gallstone disease in Japan has increased from a low level as a result of westernisation of life style, suggesting that environmental factors are important.

International prevalences of gall stones

- Very high:
  American Indians
  USA (Hispanic)
  Chile
- High:
  USA (white)
  Panama (white)
  Mexico
  United Kingdom
  Australia
  South Africa (white)
  Norway
  Denmark
  Finland
  Sweden
  Czech Republic
  Germany
  Romania
  Netherlands
  Italy
  Israel
  Taiwan
  North India
- Moderate:
  USA (black)
  Panama (black)
  South Africa (black)
  Greece
  Portugal
  Spain
  Ireland
  Singapore (Chinese)
  South India
  Japan
- Low:
  Egypt
  Zambia
  Nigeria

Various other problems can lead to gall stones. These include haemolysis (which causes an increased number of both pigment and cholesterol stones), diabetes mellitus, hypertriglyceridaemia, cirrhosis, Crohn's disease, and partial gastrectomy. Drugs such as clofibrate and, almost certainly, other fibric acid derivatives are a cause of gall stones. The most potent drug in this respect is octreotide (somatostatin analogue), used in pituitary tumours and carcinoid syndrome, which reduces gallbladder motility and increases cholesterol saturation of bile.

Primary cancer of the gall bladder is rare. It is usually seen in patients with a non-functioning gall bladder containing stones, but this association does not influence the management of gallstone disease itself. Sometimes gallbladder tumours are an incidental finding during surgery for stones. They carry a poor prognosis, but this is partly because about half of gallbladder cancer is actually metastatic. It is doubtful whether surgery influences the prognosis of macroscopically obvious primary gallbladder cancer, though some patients may be cured when the disease becomes apparent only at histological examination after cholecystectomy.

Making a diagnosis

Because gall stones are so common they have been blamed for many digestive symptoms, but they are probably innocent in most cases.[1] This concept is particularly important because ultrasonography is widely used in investigating patients and asymptomatic gall stones are often an incidental finding.

True symptoms of gall stones include acute cholecystitis (a febrile illness with pain and tenderness in the right upper quadrant), biliary colic, jaundice (often painful), and acute pancreatitis. Biliary colic is overdiagnosed. It consists of clear cut, well remembered attacks of severe upper abdominal pain lasting at least half an hour. All these patients need specific investigation, and since gall stones usually occur in the gall bladder this is the logical place to begin. The advent of ultrasonography has simplified investigation. Definite gall stones are seen as sono-dense mobile areas within the gall bladder and throw an acoustic shadow. Sometimes stones are not mobile, in which case they are not easy to discriminate from unimportant polyps, and very small ones may be missed or fail to throw a helpful acoustic shadow. Ultrasonography can also allow measurement of the diameter of the common bile duct and show the liver and hepatic bile ducts, but it can only identify with certainty about half of any stones in the common bile duct.

If the ultrasound scan findings are negative but there is a high level of suspicion, such as in a patient with upper abdominal pain and abnormal liver function tests, it is worth repeating the investigation after an interval. Liver function tests typically include raised glutamyl transferase and alkaline phosphatase activities, but the alanine aminotransferase activity may

also be affected, and the bilirubin concentration may rise in patients with acute gallbladder symptoms but no obvious bile duct problems. These findings may reflect the passage of a stone through the bile duct with transient "hold up" at the lower end. During acute symptoms the gall bladder stops functioning, at least temporarily, so that oral cholecystography is a less useful investigation. However, the investigation does have a place in evaluating equivocal cases. It may show polyps or adenomyomatosis of the gall bladder, which do not have definite clinical importance.

Fuller evaluation is needed if abnormal liver function tests or jaundice persist, in patients with acute pancreatitis, and when the common bile duct is noticeably dilated. Endoscopic retrograde cholangiopancreatography is currently the only reliable and widely available investigation for duct stones. It is not entirely without risk, but it allows therapeutic procedures to be undertaken too, when appropriate. Computed tomography is a useful alternative when filling the bile duct is unsuccessful in endoscopic retrospective cholangiopancreatography or when the procedure cannot be used for other reasons. In the future, magnetic resonance cholangiography may replace endoscopic retrograde cholangiopancreatography for diagnostic purposes. Although endoscopic ultrasonography is available, it is unlikely to be used widely because of technical implications: it is labour intensive and operator dependent.

Treatment

Biliary symptoms can be treated medically in the first instance. Biliary colic will respond to pethidine, often given with an antispasmodic agent such as atropine or glycopyrronium. Another useful treatment is diclofenac (75-150 mg) given intravenously, intramuscularly, or rectally. Where patients have acute cholecystitis, broad spectrum antibiotics are conventionally given in addition to appropriate analgesia. Empyema of the gall bladder will usually require cholecystectomy, possibly with surgical drainage too.

When gallbladder stones are proved to be the cause of severe symptoms, cholecystectomy is the best treatment for most patients. The introduction of laparoscopic cholecystectomy over the past 10 years has changed surgical practice greatly.[18] The procedure itself is associated with a more rapid return to work after what is usually a shorter hospital stay. However, there is a higher rate of bile duct injury and retained common bile duct stones than after open cholecystectomy. Because of this, many surgeons feel that peroperative cholangiography or preoperative endoscopic retrograde cholangiopancreatography are necessary. However, this is an area of controversy.

The hope of health service managers that laparoscopic cholecystectomy would reduce costs has not been realised, and the overall financial burden of surgery for gallbladder disease has not fallen. This is largely explained by the surge in operative rates, which means that many more patients are now coming to surgery. The overall morbidity and mortality associated with gallbladder surgery has not fallen.[19]

If a patient with gallbladder stones refuses surgery or is unsuitable for a general anaesthetic, alternatives may need to be considered. Bile acid therapy is an attractively safe option but is suitable for only a few patients and is unsuitable in those with severe recurrent symptoms.[20] The gall bladder must be functioning, and this can be best be shown by an oral cholecystogram. Really good results are achieved only with radiolucent stones of 5 mm or less in diameter. Stone dissolution needs to be verified by two normal ultrasound scans.[21 22] Recurrence of stones after treatment can be expected within 5 years in about 40% of patients, who may then require further treatment.[22] The best bile acid therapy currently available is probably ursodeoxycholic acid (750 mg daily), which is well tolerated and as effective as the alternatives, chenodeoxycholic acid or a combination or ursodeoxycholic and chenodeoxycholic acid. Larger stones do not respond nearly as well, and bile acid therapy is not generally advised in patients with gallbladder stones that are more than 10 mm in diameter. Bile acid therapy also has a role in stone prevention in very high risk groups. It should be given during rapid weight reduction in morbidly obese people, after bariatric surgery, and probably also to patients taking octreotide.

Alternative sophisticated treatments have been used for larger stones. External shock wave lithotripsy has been used successfully in some highly specialised centres, but this treatment often leaves fragments that have to be cleared by subsequent bile acid therapy. About one third of patients will experience colic as a direct result of external shock wave lithotripsy. Stone dissolution by percutaneous gallbladder puncture and instillation of solvents such as methyl-tertiary-butyl-ether is even more unusual.[23] This does work, but is restricted to a very few skilled operators.

Gallbladder stones rarely kill patients, but stones in the bile duct are much more serious and do carry a high morbidity and mortality. At endoscopic retrograde cholangiopancreatography it is often possible to carry out endoscopic sphincterotomy and retrieve the stones by balloon catheter or basket.[24] If the stones are too large to extract in this way, they can either be crushed with a mechanical basket lithotriptor or smashed using external shock wave lithotripsy or contact laser lithotripsy.

Neither of the two latter techniques is generally available, and if stones are too large to be removed safely, positioning of a biliary drainage stent is a useful temporary manoeuvre that alleviates problems and may be all that is required in some older patients. It is important to remember that endoscopic sphincterotomy and stone removal are not free of risk in patients who are often elderly and that mortality associated with this procedure is 1%. Where other approaches fail or are not applicable, treatment with ursodeoxycholic acid can be effective in dissolving ductal stones.

For patients with common bile duct stones who undergo open cholecystectomy, operative choledochotomy and stone extraction yield satisfactory results, though morbidity and mortality are higher than with therapeutic endoscopic retrograde cholangiopancreatography. Routine choledochoscopy at duct exploration enables the doctor to check that the stones have been cleared completely and sometimes it also facilitates their removal.

Reviews of gallbladder disease

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Gallbladder surgery cures biliary colic unless some duct stones are retained, and it largely prevents attacks of acute pancreatitis. Obviously, the patient cannot get acute cholecystitis again. The results for other symptoms are less satisfactory. One year after cholecystectomy 50% of patients complain of digestive symptoms of some kind, so it is important to ensure that their expectations are realistic before surgery.[25–27]

The 10% of patients whose symptoms do not improve at all or actually worsen after surgery are a more difficult problem. Some of these patients will be discovered to have retained, recurrent, or primary common bile duct stones and can be cured by their removal. A few patients may have biliary dyskinesia, which is improved by sphincterotomy. However, there are many other patients who remain discontented after surgery, who have no satisfactory explanation for their symptoms, and in whom treatment is generally ineffective.

As usual with medical progress, new problems emerge with changing practice. Now that gall stones can be diagnosed easily, the question is: "Do they really matter?" Most do not, and care is needed in evaluation for treatment of those that do to get the best results.

Competing interests: None declared.

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(Accepted 12 March 1999)